

IT 131571-21-6

AB: IEP (Properties).

(gene for, expression in yeast of, propn. of human insulin analogs with reduced action. in s.l. form)

LSB ANSWER 10 OF 17. HQABLOS. COPYRIGHT 2000 ACS

AN 1441:55873 HQABLOS

IN 1441:55873

TI Ionization behavior of native and mutant insulins: pK perturbation of B13-Glu in aggregated species

AU Kaarsholm, Niels O.; Havelund, Svend; Hougaard, Ingrid

CS Neye kes. Inst., Bagsvaerd, DK-2880, Den.

NO Arch. Biochem. Biophys. (1990), 263(2), 490-502

CODEN: ABBIA4; ISSN: 0003-9861

LT Journal

LA English

AB Upscale titrn. from pH 2.5 to 11.2 is used to probe solvent accessibility of ionizing groups in Zn-free preps. of native and mutant insulins. Stoichiometry and pKa values of ionizing groups in the titrn. curves are detd. by iterative curve fitting. Under denaturing conditions, the titrn. curve of human insulin is in good agreement with that predicted from the sum of unperturbed titrns. of the constituent ionizing groups and yields an apparent isoelectric point of 5.8. Under nondenaturing conditions where aggregation and pptn. occur, titrns. show that only 5 of 6 carboxylate residues of human insulin ionize in the expected region. Consequently, 1 carboxylate ionization is masked and the apparent isoelectric point is located at pH 6.4. Correlation between ionization behavior and patterns of aggregation and soly. is established by titrns. of mutant insulins and of dil. native insulin. Titrn. of an unusually sol. species, B25-Phe .fwdarw. His, shows that pptn. is not responsible for the masked carboxylate ionization of native insulin. Titrns. of mutants B13-Glu .fwdarw. Gln and B9-Ser .fwdarw. Asp show that the masked ionization probably originates from monomer-monomer interactions in the insulin dimer. Thus, the B13-Glu side chain is responsible for the masked carboxylate ionization in aggregated forms of human insulin.

IT 11061-68-0, Human insulin 72751-52-1 116094-26-9

128548-64-1

AB: PKOC (Processes).

(ionization of, mol. structure in relation to)

LSB ANSWER 11 OF 17. HQABLOS. COPYRIGHT 2000 ACS

AN 110:186795 HQABLOS

IN 110:186795

TI Human insulin analogs and injectable solutions containing these analogs and zinc ions with prolonged antidiabetic action.

IN Markussen, Jan; Norris, Klem; Lundgren, Ingrid

LA N. v. Insulin A/S, Den.

CS Eur. Pat. Appl., 1989

CIPK: FIKKX

LT Patent

LA English

FORM: 4

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|------------|------|-----------|-----------------|-----------|
| 11 | EP 344516 | A | 1989.11.7 | EP 344516 | 1989.11.7 |
| | EP 344517 | A | 1989.11.7 | EP 344517 | 1989.11.7 |
| | EP 344518 | A | 1989.11.7 | EP 344518 | 1989.11.7 |

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|----------------------|-------------|---------------|--------------|
| AD 612324 | BE 13410711 | | |
| GN 87104989 | A 13880337 | UN 1447-14488 | 14870720 --- |
| ZA 8705295 | A 1444447 | GA 1447-1448 | 14870721 --- |
| HU 45271 | A2 14480688 | HY 1447-1448 | 14870722 --- |
| HU 203371 | B 14910729 | | |
| DD 273839 | A5 14891129 | ED 1447-14481 | 14870723 --- |
| UC 4946828 | A 14900807 | US 1447-14487 | 14870724 --- |
| IL 85243 | A1 14930114 | IL 1447-14483 | 14870725 --- |
| AT 49699 | E 14940115 | AT 1447-14484 | 14870726 --- |
| ES 2061504 | T3 14941216 | ES 1447-14485 | 14870727 --- |
| JF 63099096 | A2 14980430 | JP 1447-14486 | 14870728 --- |
| GS 5008241 | A 14910416 | US 1447-14488 | 14870729 --- |
| FRAI DK 1986-3470 | 19860721 | <-- | |
| DK 1985-1135 | 19850312 | <-- | |
| DK 1986-1070 | 19860316 | <-- | |
| US 1986-858472 | 19860311 | <-- | |
| DK 1987-948 | 19870225 | <-- | |
| EP 1987-306405 | 19870720 | <-- | |
| US 1987-15550 | 19870720 | <-- | |
| GS MARPAT 110:196795 | | | |
| GI | | | |

A(1-3)-E1-A(5-6)-Cys-A(8-16)-E2-A(18-19)-Cys-E

S S
S S

B(1-6)-Cys-B(8-12)-E3-B(14-16)-Cys

K-Z_n-Y_m-Lys-Pro-X-B(20-22)-E4-Gly 1

AB Insulin derivs. having a pos. charge compared with that of human insulin at neutral pH are used to prep. solns. having prolonged insulin action. These insulin derivs. have the structure I (A and B followed by pos. in parentheses designate peptide fragments of A and B chains, resp.; E1-E4 = Glu, neutral amino acid; X = Thr, Arg, Lys; Y, Z = amino acid in which any side-chain NH2 may be acylated and any side-chain OH may be alkylated; m, n = 0, 1; R = OH, amide or ester or a 1-alkyl-2-oxo-3-oxo-4-oxo-5-oxo-6-oxo-7-oxo-8-oxo-9-oxo-10-oxo-11-oxo-12-oxo-13-oxo-14-oxo-15-oxo-16-oxo-17-oxo-18-oxo-19-oxo-20-oxo-21-oxo-22-oxo-23-oxo-24-oxo-25-oxo-26-oxo-27-oxo-28-oxo-29-oxo-30-oxo-31-oxo-32-oxo-33-oxo-34-oxo-35-oxo-36-oxo-37-oxo-38-oxo-39-oxo-40-oxo-41-oxo-42-oxo-43-oxo-44-oxo-45-oxo-46-oxo-47-oxo-48-oxo-49-oxo-50-oxo-51-oxo-52-oxo-53-oxo-54-oxo-55-oxo-56-oxo-57-oxo-58-oxo-59-oxo-60-oxo-61-oxo-62-oxo-63-oxo-64-oxo-65-oxo-66-oxo-67-oxo-68-oxo-69-oxo-70-oxo-71-oxo-72-oxo-73-oxo-74-oxo-75-oxo-76-oxo-77-oxo-78-oxo-79-oxo-80-oxo-81-oxo-82-oxo-83-oxo-84-oxo-85-oxo-86-oxo-87-oxo-88-oxo-89-oxo-90-oxo-91-oxo-92-oxo-93-oxo-94-oxo-95-oxo-96-oxo-97-oxo-98-oxo-99-oxo-100-oxo-101-oxo-102-oxo-103-oxo-104-oxo-105-oxo-106-oxo-107-oxo-108-oxo-109-oxo-110-oxo-111-oxo-112-oxo-113-oxo-114-oxo-115-oxo-116-oxo-117-oxo-118-oxo-119-oxo-120-oxo-121-oxo-122-oxo-123-oxo-124-oxo-125-oxo-126-oxo-127-oxo-128-oxo-129-oxo-130-oxo-131-oxo-132-oxo-133-oxo-134-oxo-135-oxo-136-oxo-137-oxo-138-oxo-139-oxo-140-oxo-141-oxo-142-oxo-143-oxo-144-oxo-145-oxo-146-oxo-147-oxo-148-oxo-149-oxo-150-oxo-151-oxo-152-oxo-153-oxo-154-oxo-155-oxo-156-oxo-157-oxo-158-oxo-159-oxo-160-oxo-161-oxo-162-oxo-163-oxo-164-oxo-165-oxo-166-oxo-167-oxo-168-oxo-169-oxo-170-oxo-171-oxo-172-oxo-173-oxo-174-oxo-175-oxo-176-oxo-177-oxo-178-oxo-179-oxo-180-oxo-181-oxo-182-oxo-183-oxo-184-oxo-185-oxo-186-oxo-187-oxo-188-oxo-189-oxo-190-oxo-191-oxo-192-oxo-193-oxo-194-oxo-195-oxo-196-oxo-197-oxo-198-oxo-199-oxo-200-oxo-201-oxo-202-oxo-203-oxo-204-oxo-205-oxo-206-oxo-207-oxo-208-oxo-209-oxo-210-oxo-211-oxo-212-oxo-213-oxo-214-oxo-215-oxo-216-oxo-217-oxo-218-oxo-219-oxo-220-oxo-221-oxo-222-oxo-223-oxo-224-oxo-225-oxo-226-oxo-227-oxo-228-oxo-229-oxo-230-oxo-231-oxo-232-oxo-233-oxo-234-oxo-235-oxo-236-oxo-237-oxo-238-oxo-239-oxo-240-oxo-241-oxo-242-oxo-243-oxo-244-oxo-245-oxo-246-oxo-247-oxo-248-oxo-249-oxo-250-oxo-251-oxo-252-oxo-253-oxo-254-oxo-255-oxo-256-oxo-257-oxo-258-oxo-259-oxo-260-oxo-261-oxo-262-oxo-263-oxo-264-oxo-265-oxo-266-oxo-267-oxo-268-oxo-269-oxo-270-oxo-271-oxo-272-oxo-273-oxo-274-oxo-275-oxo-276-oxo-277-oxo-278-oxo-279-oxo-280-oxo-281-oxo-282-oxo-283-oxo-284-oxo-285-oxo-286-oxo-287-oxo-288-oxo-289-oxo-290-oxo-291-oxo-292-oxo-293-oxo-294-oxo-295-oxo-296-oxo-297-oxo-298-oxo-299-oxo-300-oxo-301-oxo-302-oxo-303-oxo-304-oxo-305-oxo-306-oxo-307-oxo-308-oxo-309-oxo-310-oxo-311-oxo-312-oxo-313-oxo-314-oxo-315-oxo-316-oxo-317-oxo-318-oxo-319-oxo-320-oxo-321-oxo-322-oxo-323-oxo-324-oxo-325-oxo-326-oxo-327-oxo-328-oxo-329-oxo-330-oxo-331-oxo-332-oxo-333-oxo-334-oxo-335-oxo-336-oxo-337-oxo-338-oxo-339-oxo-340-oxo-341-oxo-342-oxo-343-oxo-344-oxo-345-oxo-346-oxo-347-oxo-348-oxo-349-oxo-350-oxo-351-oxo-352-oxo-353-oxo-354-oxo-355-oxo-356-oxo-357-oxo-358-oxo-359-oxo-360-oxo-361-oxo-362-oxo-363-oxo-364-oxo-365-oxo-366-oxo-367-oxo-368-oxo-369-oxo-370-oxo-371-oxo-372-oxo-373-oxo-374-oxo-375-oxo-376-oxo-377-oxo-378-oxo-379-oxo-380-oxo-381-oxo-382-oxo-383-oxo-384-oxo-385-oxo-386-oxo-387-oxo-388-oxo-389-oxo-390-oxo-391-oxo-392-oxo-393-oxo-394-oxo-395-oxo-396-oxo-397-oxo-398-oxo-399-oxo-400-oxo-401-oxo-402-oxo-403-oxo-404-oxo-405-oxo-406-oxo-407-oxo-408-oxo-409-oxo-410-oxo-411-oxo-412-oxo-413-oxo-414-oxo-415-oxo-416-oxo-417-oxo-418-oxo-419-oxo-420-oxo-421-oxo-422-oxo-423-oxo-424-oxo-425-oxo-426-oxo-427-oxo-428-oxo-429-oxo-430-oxo-431-oxo-432-oxo-433-oxo-434-oxo-435-oxo-436-oxo-437-oxo-438-oxo-439-oxo-440-oxo-441-oxo-442-oxo-443-oxo-444-oxo-445-oxo-446-oxo-447-oxo-448-oxo-449-oxo-450-oxo-451-oxo-452-oxo-453-oxo-454-oxo-455-oxo-456-oxo-457-oxo-458-oxo-459-oxo-460-oxo-461-oxo-462-oxo-463-oxo-464-oxo-465-oxo-466-oxo-467-oxo-468-oxo-469-oxo-470-oxo-471-oxo-472-oxo-473-oxo-474-oxo-475-oxo-476-oxo-477-oxo-478-oxo-479-oxo-480-oxo-481-oxo-482-oxo-483-oxo-484-oxo-485-oxo-486-oxo-487-oxo-488-oxo-489-oxo-490-oxo-491-oxo-492-oxo-493-oxo-494-oxo-495-oxo-496-oxo-497-oxo-498-oxo-499-oxo-500-oxo-501-oxo-502-oxo-503-oxo-504-oxo-505-oxo-506-oxo-507-oxo-508-oxo-509-oxo-510-oxo-511-oxo-512-oxo-513-oxo-514-oxo-515-oxo-516-oxo-517-oxo-518-oxo-519-oxo-520-oxo-521-oxo-522-oxo-523-oxo-524-oxo-525-oxo-526-oxo-527-oxo-528-oxo-529-oxo-530-oxo-531-oxo-532-oxo-533-oxo-534-oxo-535-oxo-536-oxo-537-oxo-538-oxo-539-oxo-540-oxo-541-oxo-542-oxo-543-oxo-544-oxo-545-oxo-546-oxo-547-oxo-548-oxo-549-oxo-550-oxo-551-oxo-552-oxo-553-oxo-554-oxo-555-oxo-556-oxo-557-oxo-558-oxo-559-oxo-560-oxo-561-oxo-562-oxo-563-oxo-564-oxo-565-oxo-566-oxo-567-oxo-568-oxo-569-oxo-570-oxo-571-oxo-572-oxo-573-oxo-574-oxo-575-oxo-576-oxo-577-oxo-578-oxo-579-oxo-580-oxo-581-oxo-582-oxo-583-oxo-584-oxo-585-oxo-586-oxo-587-oxo-588-oxo-589-oxo-590-oxo-591-oxo-592-oxo-593-oxo-594-oxo-595-oxo-596-oxo-597-oxo-598-oxo-599-oxo-600-oxo-601-oxo-602-oxo-603-oxo-604-oxo-605-oxo-606-oxo-607-oxo-608-oxo-609-oxo-610-oxo-611-oxo-612-oxo-613-oxo-614-oxo-615-oxo-616-oxo-617-oxo-618-oxo-619-oxo-620-oxo-621-oxo-622-oxo-623-oxo-624-oxo-625-oxo-626-oxo-627-oxo-628-oxo-629-oxo-630-oxo-631-oxo-632-oxo-633-oxo-634-oxo-635-oxo-636-oxo-637-oxo-638-oxo-63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 120249-36-7P 120249-37-8P 120249-38-9P
 120249-40-3P 120249-41-4P 120249-43-6P
 120249-45-8P 120249-46-9P 120249-47-0P
 120249-49-2P 120249-50-5P 120249-51-6P
 120249-53-8P 120249-55-0P 120249-57-2P
 120249-58-3P 120249-59-4P 120249-61-8P
 120249-62-9P 120249-63-0P 120249-64-1P
 120249-66-3P 120249-68-5P 120249-69-6P

KL: PREP (Preparation)

(prepn. of, as antidiabetic)

IT 11061-68-ODP, Human insulin, analogs

KL: PREP (Preparation)

(prepn. of, as antidiabetics)

IT 120249-72-1 120249-74-3 120249-75-4

120249-76-5 120249-77-6 120249-79-8

120249-80-1 120249-81-2

KL: RCT (Reactant)

(transpeptidation of, in prepn. of human insulin analog)

158 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2000 ACM

AN 1988:596998 HCAPLUS

LN 109:196998-

TI Soluble, prolonged-acting insulin derivatives. II. Degree of protraction, crystallizability and chemical stability of insulins substituted in positions A21, E13, B23, B27 and B30

AU Markussen, J.; Diers, I.; Hougaard, P.; Langkjaer, L.; Norris, K.; Snel, L.; Soerensen, A. R.; Soerensen, E.; Voigt, H. O.

CS Novo Res. Inst., Bagsvaerd, 2880, Den.

CO Protein Eng. (1988), 2(2), 157-66

COEN: PRENEP; LANN: Low-Lies

IT Journal

LA English

AB It was previously demonstrated that insulins to which pos. charge has been added by substituting E13 glutamic acid with a threonine residue, B-threonine with an arginine or lysine residue, and by blocking the C-terminal carboxyl group of the B-chain by amidation, featured a prolonged absorption from the subcutis of rabbits and pigs after injection in skin at acidic pH. The phenomenon is ascribed to a low soly. combined with the readiness by which these analogs crystallize as the injected insulin is neutralized in the tissue. However, analogs ins. of insulin are chem. unstable as A13 aspartate is the most labile aspartic acid and takes part in a reaction of transamidation with the aspartamide groups of other ins. In order to overcome the instability, modifications were introduced using aspartic acid, in addition to those in E13, B27 and B30, challenging the fact that A13 aspartate has been conserved in this position throughout the evolution. Biol. potency was retained when glycine, serine, threonine, aspartic acid, histidine and arginine were introduced in this position, although a varying degree. In the crystal structure of insulin (1988) and also in the sequence of E13, A13, B27 and B30, the aspartic acid residue is conserved. It is suggested that the aspartic acid residue is a key residue in the

analogs with Asn₁ glycine showed first-order absorption kinetics in pigs with a half-life of approx. 1 h, independent of the dose admin. The day-to-day variation of the absorption of this analog was significantly lower than that of the conventional insulin suspensions, a property that might render such an insulin useful in the attempts to improve glucose control in diabetics by a more predictable delivery of basal insulin.

IT 11061-68-0 117442-95-2 117442-97-4
117442-99-6 117443-02-4 117443-05-7

RL: BIOL (Biological study)

(insulin deriv. precursor, yields of, relative to ferment. biomass)

IT 117442-94-1P 117442-96-3P 117442-98-5P
117443-00-2P 117443-01-3P 117443-03-5P
117443-04-6P 117443-06-8P 117443-07-9P
117443-08-0P 117443-09-1P 117443-10-4P

RL: SYN (Synthetic preparation); PREP (Preparation)

(prepn. and biol. activity and properties of prolonged-acting)

IT 7440-66-6, Zinc, biological studies

RL: BIOL (Biological study)

(substituted insulin derivs. biol. activity and stability in relation to)

15- ANSWER 13 OF 17 HQAPLUS COPYRIGHT 1988 ACI

AN 1000:504909 HQAPLUS

EN 100:104909

TI Monomeric insulins obtained by protein engineering and their medical implications

AU Brange, J.; Ribel, U.; Hansen, J. F.; Dodson, G.; Hansen, M. T.;

Havelund, S.; Melberg, S. G.; Norris, F.; Norris, K.; et al.

CS Novo Res. Inst., Novo Alle, Bagsvaerd, DK-2880, Den.

SO Nature (London) (1988), 333(6174), 679-82

CODEN: NATUAS; ISSN: 0028-0836

DT Journal

LA English

AB By single amino-acid substitutions, insulins were prepd. which are essential monomeric at pharmaceutical concns. (0.6 mM) and which have largely preserved their biol. activity. These monomeric insulins are absorbed 2-4-fold faster after s.c. injection than the present rapid-acting insulins. They are tested as a possible giving diabetic patients a more physiol. plasma insulin profile at the time of meal consumption.

IT 7440-66-6D, Zinc, complexes with insulin

RL: PRE (Properties)

(bioavailability and biol. activity and self assocn. of)

IT 11061-68-0 11061-68-0D, zinc complexes
12584-58-6D, zinc complexes 55599-09-2
111479-48-2 116094-19-0 116094-20-3
116094-21-4 116094-23-6 116094-25-8
116094-26-9 116094-27-0 116094-28-1
116094-29-2

RL: BIOL (Biological study)

(biol. activity and bioavailability and self-assocn. and activity of)

15- ANSWER 14 OF 17 HQAPLUS COPYRIGHT 1988 ACI

AN 1000:126727 HQAPLUS

EN 100:126727

TI A study of the effect of zinc on the stability and activity of insulin in the presence of ascorbic acid and the effect of zinc on the stability and activity of insulin in the presence of ascorbic acid

IT 12584-58-6, Porcine insulin 98743-24-9

(derivs. presn. from, as prolonged action derivs.)

113190-02-6P 113190-03-7P 113190-11-7P

KL: RCT (Reactant); SPN (Synthetic preparation); PHEP (Preparation; prepn. and deprotection of)

IT 74870-09-0P 80449-79-2P 81959-12-8P

97396-48-0P 110068-63-8P 110068-65-0P

110068-80-9P 110084-28-1P 113189-92-7P

113189-96-1P 113189-97-2P 113190-00-4P

113190-01-5P 113190-07-1P 113190-08-2P

113190-09-3P 113190-10-6P

EL: SSN (Synthetic preparation); FREF (Preparation)

(prepn. and protraction and crystallizability of, as prolonged-acting insulins)

113189-88-1P 113189-89-2P 113189-95-0P

FI: 2011 - Synthetische Katalysatoren; 2012 - Katalysatoren

RECEIVED: 1987-07-17

113190-14-0P 113314-96-8P 113610-16-5P

BL: SPN (Synthetic preparation); PHEP (Preparation)

(prepn. and transpiration of, with the other parts)

113190-12-8P

FL: SPN (Synthetic preparation); IREP (Preparation)

(prepn. of)

ANSWER 15 OF 17: HADLEY - 100% CORRECT

the 1990s, the number of people in the world who are under 15 years of age is expected to increase from 1.1 billion to 1.5 billion. The number of people aged 65 and over is expected to increase from 200 million to 400 million. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion. The number of people aged 15 and over is expected to increase from 3.5 billion to 4.5 billion.

1000

Markussen, Jan

Markussen, San

[illegible]

THE UNIVERSITY OF CHICAGO

1. $\frac{1}{2}$ 2. $\frac{1}{2}$ 3. $\frac{1}{2}$ 4. $\frac{1}{2}$ 5. $\frac{1}{2}$ 6. $\frac{1}{2}$ 7. $\frac{1}{2}$ 8. $\frac{1}{2}$ 9. $\frac{1}{2}$ 10. $\frac{1}{2}$

12. English.

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

$$A(1-v) = E^I - A(v-v) = (v_0 - A(8-16)) = E^I - A(8-16) = (v_0 - A(8-16))$$

E(1-6)-Cys-E(8-12)-E³-E(14-18)-Cys
R-E₂-I₂-Lys-Ile-H-E(20-22)-E⁴-Gly

A1 The title compds. [I; A and B are insulin A- and B-chain peptide fragments, resp.; E1-E4 = Glu, neutral amino acid residues; X = L-Thr, L-Arg, L-Lys; Y, Z = amino acids (old chain) or glycylglycyl-, D-alanyl-, D-glutamyl-, D-prolyl-, or L-leucyl-, useful to prep. injectable solns. with prolonged insulin action, were prepd. These preps. may contain Zn²⁺, preferably at 5-200 μm./ml. ArgBPC-NH2 human insulin was prepd. by transpeptidation of H-Arg-NH2 with γ-glu-insulin in the presence of triethylamine.

7440-66-6, Zinc, [illegible]

11061-68-ODP, Bureau Building, Room 12584-58-6DP,
Building 100, Room 81959-12-8P 110068-58-1P
110068-59-2P 110068-60-5P 110068-61-6P
110068-62-7P 110068-63-8P 110068-64-9P
110068-65-0P 110068-67-2P 110068-68-3P
110068-69-4P 110068-70-7P 110068-72-9P
110068-73-0P 110068-74-1P 110068-75-2P
110068-78-5P 110068-79-6P 110068-80-9P
110068-83-2P 110084-28-1P

IN 101:178756
 TI Semisynthesis of human insulin.
 AU Markussen, Jan
 OS Novo Ind., Bagsvaerd, Den.
 JO Methods Diabetes Res. (1984), Volume 1, Issue A, 4-11.
 Editor(s): Larner, Joseph; Ichi, Stephen L. Publisher: Wiley, New York, N. Y.
 COLEN: 53BDAa
 DT Conference
 LA English
 AB Methods are described for the semisynthesis of human insulin [11061-68-0] from porcine insulin [12584-58-6], in which des(Ala30) porcine insulin [39416-73-4] (formed by 2 different routes) is reacted with various threonine esters. Deprotection of the resulting insulin esters yields human insulin mole. (containing a threonine residue in the cuboxyl terminal position of the beta-chain).
 IT 12584-58-6
 RL: BIOL (Biological study)
 (human insulin prepn. from)
 IT 74870-09-0P 76688-23-8P 80449-79-2P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and deprotection of)
 IT 7440-66-6DP, complexes with insulin 11061-68-ODP,
 zinc complexes 11061-68-0P 39416-73-4DP,
 zinc complexes
 RL: SPN (Synthetic preparation); IREP (Preparation)
 (prepn. of)
 IT 39416-73-4
 RL: RCT (Reactant)
 (reaction of, with threonine esters)

L88 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2000 ACS
 AN 1983:8177 HCAPLUS
 DN 98:8177
 TI Stabilized insulin preparations
 IN Brange, Jens Jorgen Veilgaard; Havelund, Svend
 PA Novo Industrial A/S, Den.
 JO Eur. Pat. Appl., 1983.
 COLEN: EPXXDW
 DT Patent
 LA English
 AB.

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|-------------------|------|-----------|-----------------|------------|
| B1 | EP 60141 | A2 | 19820919 | EP 1982-00141 | 1982-09-19 |
| | EP 60141 | A1 | 1982-0919 | | |
| | EP 60141 | B1 | 1982-0919 | | |
| | A: AT, DE, NL, SE | | | | |
| | DA 1982-0919 | A | 1982-0919 | DA 1982-0919 | 1982-09-19 |
| | AT 1982-0919 | B | 1982-0919 | AT 1982-0919 | 1982-09-19 |
| | AT 1982-0919 | A1 | 1982-0919 | | |
| | BE 892413 | A1 | 1982-0919 | BE 1982-0919 | 1982-09-19 |
| | DK 820107A | A | 1982-0919 | DK 1982-0919 | 1982-09-19 |
| | DK 144833 | B | 1982-0919 | | |
| B2 | DK 144833 | C | 1982-0919 | | |
| | DK 144833 | A | 1982-0919 | DK 1982-0919 | 1982-09-19 |
| | DK 144833 | B | 1982-0919 | | |
| | DK 144833 | C | 1982-0919 | | |

UC 4471116 A 19940816 UC 1994-199447 19940816 ---
 CH 452031 A 19941031 CH 1994-1447 19941031 ---
 AT 23209 E 19941111 AT 1994-1107 19941111 ---
 FI 78836 E 19940631 FI 1994-1111 19940631 ---
 FI 78838 C 19940101
 IRAI GB 1981-7428 19810810 ---
 DK 1981-4148 19810918 ---
 EP 1982-501207 19820808 ---
 AB Stabilized **zinc** insulin [1944-62-5] prepn. for use in equipment
 for continuous insulin deliver, comprises a Zn or Mg salt, a preservative,
 and optionally, a nonionizing osmotic pressure controlling agent and/or a
 pH buffering agent which does not form a complex with either Ca or Mg ions
 in addn. to insulin. Thus, cryst. monocomponent porcine insulin (0.44 g/
 contg. 0.4 Zn with a total activity of 200,000 IU was dissolved
 in 150 mL H₂O contg. HCl (0.5 mL N), to this was added 100 mL H₂O contg.
 glycerol and PhOH 6.4 and 0.8 g, resp., the pH was adjusted with NaOH to
 7.5, and the total vol. increased to 400 mL with H₂O. To 100 mL of this
 soln. was added 29.4 mg CaCl₂ and the soln. sterilized by filtration and
 transferred aseptically to 10 mL vials. The soln. contg. 500 IU
 insulin/mL in 2 times, 10-3M soln. CaCl₂ had a stability factor 95.
 IT 11061-68-0D, **zinc** complexes
 RL: BIOL (Biological study)
 (semi-synthetic, stable compn. contd. calcium or magnesium salts and)
 IT 12584-58-6D, **zinc** complexes
 RL: BIOL (Biological study)
 (stable compn. contg. calcium or magnesium salts)

→ a 159 bib abs hitin tot

L59 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2010 ACS
 AN 1994:646581 HCAPLUS
 DN 121:246581
 TI Structural Asymmetry and Half-Site Reactivity in the T to R Allosteric
 Transition of the Insulin **Hexamer**
 AU Brzovic, Peter S.; Choi, Eunhee P.; Brzovic, Jan; Karsch, Niels G.;
 Dunn, Michael P.
 U Department of Biochemistry, University of California, Riverside, CA,
 92521-0129, USA
 SO Biochemistry (1994), 33(44), 13957-69
 JFBI: BIOCHEM; ISSN: 0006-2944
 JI Journal
 LA English
 AB The **zinc**-insulin **hexamer**, the storage form of insulin
 in the pancreas, is an all- α -helical protein capable of undergoing
 transitions between three distinct conformational states, designated T,
 R₁, and R₂, on the basis of their ligand-binding properties, all-steric
 behavior, and protein symmetry. R. A. Kinsman, et al. (1994).
 The transition from the T-state to the R-state involves a shift in the
 position of the C-terminus of the B-chain within the zinc-binding site
 displaced by approximately 1.5 Å. This motion is accompanied by small
 changes in the positions of A-chain residues and other B-chain residues.
 In this paper, the amino-terminal (N¹) and N² (N²) residues are used
 to characterize the ligand-induced T to R transition of wild-type and
 88Le mutant human **zinc**-insulin **hexamers** and to study
 the effect of the 88Le mutation on the T to R transition. The results show
 that the 88Le mutation does not affect the T to R transition.

distribution of **hexamer** conformations in favor of the R-state with the order of effectiveness, T3N- > N3- > N3N3- > T3N3- > T3N3N3-. Anal. of one- and two-dimensional spectra indicate that with wild-type insulin, T3N- and N3- give T3R3 species, whereas the E3L3 mutant gives an R3 species. An allosteric model for the insulin T to R transition based on the structural asymmetry model [F. Heydoux, et al. (1974)] is proposed that explains the neg. and pos. allosteric properties of the system, including the role of T3R3 and the action of homotropic and heterotropic effectors.

IT 72751-52-1, 13P-3in-human insulin

RI: PRP (Properties)

(Insulin **hexamer** structural asymmetry and half-site reactivity in allosteric transition)

LI ANSWER 2 OF 36 HEAVILY CRYPTICHT 1993 ACT

AN 1993:491195 HEAVILY

DN 121:1185

TI A new structural type of **zinc** insulin observed in a mutant of [A21,Ser]-human insulin

AB Wang, Da-cheng; Zeng, Zhong-hao; Hu, Yong-lin; Markusen, Jan

CS Inst. Biophys., Chin. Acad. Sci., Beijing, 100001, Peop. Rep. China

CP Rept.: Biol. Chem., Proc. Chin. Acad. Sci., 1993, Beijing

DA 1993, 241-4. Editor(s): Du, Yu-rang; Tam, James P.; Zhang, You-shang. Publisher: ESCOM, Leiden, Neth.

CODEN: 59YOAI

BT Conference

LA English

AB The **hexameric zinc** insulin structure obsd. in the [A21,Ser]-human insulin crystal represents a new type of T3R3 insulin conformational state (T3R3), in which the conformational pattern of the subunits are basically T3R3, except for a nonhelical stretch of E1-E3, but the coordination mode of **zinc** ions in the metal chelate sites adopts a T6-like type, namely 2 **zinc** ions are all on the 3-fold axis and both possess 6 ligands arranged as an octahedral array. In the E-3 structure, 6 coordination sites of **zinc** ion(II) are all occupied by the residues of insulin mol. itself, including 3 Asn-E3 and 3 His-E1, which has not yet been obsd. in other **hexameric** insulin structures. The coordinate interactions between Asn-E3 and Zn(II) should be a significant factor for stabilizing the helical conformation of E4-E9 segment. It seems likely that the T3R3 structure represents a transitional state intermediate in the T to R conformational transition, which may provide a new model for the investigation of the allosteric transition of insulin. A neutral org. mol., 1,4-dioxane, present in crystn. media is most probably the effector of R3 conformation, which binds to a pocket on the **hexamer** surface and induces the conformational transition from T3R3 to R3.

IT 134091-11-5D, hexamers, 13P-3in-human insulin with zinc

RI: IMI (Properties)

(Insulin **hexamer** structural asymmetry and half-site reactivity in allosteric transition)

LI ANSWER 2 OF 36 HEAVILY CRYPTICHT 1993 ACT

AN 1993:491195 HEAVILY

DN 121:1185

TI Crystallographic Evidence for Partial Coordination of Zinc in the T3R3 Human Insulin **Hexamer**

AB Wang, Da-cheng; Zeng, Zhong-hao; Hu, Yong-lin; Markusen, Jan

CS Inst. Biophys., Chin. Acad. Sci., Beijing, 100001, Peop. Rep. China

CP Rept.: Biol. Chem., Proc. Chin. Acad. Sci., 1993, Beijing

hexamer
insulin
zinc ions.

ANS. The structure has been refined to a residual of 0.17% using 2000 independent data points to 1.4-Å resolution. The asym. unit consists of a T₃ dimer, and the insulin **hexamer** is generated by the action of the crystallized 3-fold axis. The conformation of one insulin trimer is nearly identical to that of the T₀ **hexamer**, while the other trimer approximates that of the R₀ **hexamer**, except for the three N-terminal B-chain residues that adopt an extended rather than an α -helical conformation. Each of the two **zinc** ions, which lie on the crystallizing 3-fold axis and exhibit two different, disordered coordination geometries, is coordinated by the imidazole groups of three symmetry-related B10 histidine residues. The coordination sphere of the **zinc** in the T₃ trimer is either tetrahedral, with the fourth site filled by a chloride ion, or octahedral, completed by three water mols. The coordination of the **zinc** in the 12-ÅNS narrow channel in the R₀ trimer is tetrahedral, with either a second chloride ion or a water mol. completing the coordination sphere. The putative off-axial **zinc** binding sites that result from the T₁ to R₀ transition of monomer II do not contain **zinc** ion, but instead are filled with clusters of ordered water mols. The observation that the T-state trimer contains **zinc** in both tetrahedral and octahedral geometries has important implications for the interpretation of spectroscopic results.

IT 11061-68-OD, Human insulin, **zinc** complexes,

hexamers

RL: PRP (Properties)

(crystal structure of, for T₃R₃ conformation with dual coordination)

IT 7440-66-6D, **Zinc**, complexes

RL: BIOL (Biological study)

(with human insulin **hexamer** T₃R₃, crystal structure of)

L59 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 1993 ACS

AN 1994:722 HCAPLUS

DN 120:722

TI Distinction of structural reorganization and ligand binding in the T₁ to R₀ transition of insulin on the basis of allosteric models

AU Jacoby, Edgar; Krueger, Peter; Karatas, Yasar; Wellmer, Axel

CS Inst. Biochem., Rheinisch-Westfälische Tech. Hochschule, Aachen, Germany

JS Biol. Chem. Hoppe-Seyler (1993), 274:8, 1-11

INDEX: BIOSIS; ISSN: 0177-3893

ET Journal

LA English

AB The structural model is presented for the T₁ to R₀ transition of insulin **hexamers** in the presence of phenolic ligands which are based on existing exptl. information. The transition mainly involves residues 1-8 of the B-chain, i.e. 15% of the mol., which are extended in the T₁ and helical in the R₀ state. The main structural reorganization are the transition from a monomer to a trimer; the transition of the monomer trimer is characterized compared to the first step, the transition of a trimer to a **hexamer** transition in a separate process; structural changes upon ligand binding only exist in the trimer; ligands enter the cavity by approaching the B-chain; the ligand is accommodated in a pocket made up between two adjacent subunits; binding of ligand mol. extends the lifetime of the two other binding sites of a trimer; only ligand-free trimers can undergo transition. The two models allowed for UV spectroscopic titration of **zinc** and small insulin with phenol and monomer can be induced in terms of transition of monomer to a dimer, dimer to a trimer, and trimer to a **hexamer**. The structural model is consistent with the experimental data.

11061-68-OD.

hexamers

Zn-induced insulin hexamer formation. The formation of monomeric insulin through amino acid replacements was accompanied by conformational changes that may be the cause for decreased action. It is demonstrated that self-association of insulin can be drastically altered by substitution of one or two key amino acids.

IT 11061-68-0, Human insulin 116094-23-6

133107-40-1 133107-45-6 133107-52-5

133107-64-9 144637-14-9 144637-15-0

KE: Ikk (Properties)

(cell assocn. of, C-terminal amino acid role in)

END ANSWER 7 OF 16 HCABLOS COPYRIGHT 2000 ACS

AN 1001:4e55e0 HCABLOS

DN 115:555e0

TI Disposition of the phenylalanine B25 side chain during insulin-receptor and insulin-insulin interactions

AF Mirmira, Raghavendra G.; Tader, Howard J.

CP Dep. Biochem. Mol. Biol., Univ. Chicago, Chicago, IL, U.S.A., USA

AO Biochemistry (1991), 30(23), 4220-4

COPEN: BICHAW; ISSN: 0006-2960

BT Journal

LA English

AB By using the semisynthesis of both full-length insulin analogs and their des-pentapeptide-(B20-B30)-L-alpha.-carboxamide counterparts, the importance of the electronic character and bulk of the position B25 side chain both in directing insulin interaction with its receptor on isolated canine hepatocytes and in netg. the ability of insulin to self-assoc. in soln. was examd. Analogs include those in which InsB25 was replaced by cyclohexyl-Ala; Tyr; p-nitro-, p-fluoro-, p-isole-, or p-amino-Phe; or p-amino-Phe in which the arom. amine function has been acylated by the acetyl, hexanoyl, decanoyl, or 1-admantanoyl group. Findings identify that (a) the .beta.-arom. side chain at position B25 is indeed crit. for high-affinity ligand-receptor interactions, (b) neither electron withdrawal from nor electron donation to the .beta.-arom. ring perturbs ligand-receptor interactions in major ways, and (c) considerable latitude is allowed the placement of linear or polycyclic apolar mass at the para position in p-amino-InsB25-substituted analogs with respect both to receptor binding ability and self-ability in vivo, and (d) para apolar mass at position B25 is readily accommodated during the self-assocn. of insulin monomers, as assessed by anal. tyrosine radioiodination and spectroscopic anal. of insulin complexes. The anal. data obtained are discussed in terms of a model for insulin-receptor interactions at the cell membrane in which the position B25 side chain defines the edge of intermol. contact.

IT 103370-34-9 135393-09-8 135393-10-1

135393-11-2 135393-12-3 135393-13-4

135393-14-5 135393-15-6 135393-16-7

135393-17-8 135393-18-9 135393-19-0

135393-20-3 135393-21-4 135393-22-5

135393-23-6 135393-24-7 135393-25-8

135393-26-9 135393-27-0

KE: PIR (Biological process); IPI (Properties); PIR (Chemical structure);

IPRO (Process)

(receptor binding of, B25 side chain interaction)

END ANSWER 8 OF 16 HCABLOS COPYRIGHT 2000 ACS

AN 1001:4e55e0 HCABLOS

DN 115:555e0

AB For-hexapeptide- $[B_{29-31}]$ insulin-B₁₋₄-d-erythro-threo-phenylethylamide (II) was synthesized, and this α -carboxy-hexapeptide-insulin was fully as active as infant insulin in blood glucose-lowering and mouse convulsion tests. Although the formation of high-mol.-wt. aggregates of human insulin were dependent on Zn²⁺, the aggregation of I was Zn²⁺-independent. Thus, the complete B chain and its terminus of insulin were not required for insulin activity, but they were important in the formation of stable hexamers with Zn²⁺ and in the formation of insulin polymers.

RL: SPN (Synthetic preparation); FREI (Preparation)
(prepn. and biol. activities and preventive, oil

English.
AB Mol. wts. and wt. distributions of sulfated, Zn-free, and 27n insulins have been measured at pH 7.3 as a function of concn. from 0.1 to 2 mg/mL by use of a combination of light scattering, refractometry, and size-exclusion chromatog. Results show that sulfated insulin is monomeric over the studied concn. range. Wt. av. mol. wts. between those of a monomer and a **hexamer** were found for both zinc-free and 27n insulins. Zinc stabilizes the **hexamer**, and the dimer-hexamer equil. const. is approx. 400 times higher in the presence of Zn than in its absence. An av. hydrodynamic radius of 5.6 nm, close to the crystallog. size of the insulin **hexamer**, was detd. from dynamic light scattering of 27n insulin sols.

3L: IRP (Properties)
(sol. descom. of, in neutral solns.)

10 The self-assembled Zn²⁺-insulin hexamer, Zn²⁺-
insulin analog His₁₀glutamine, γ -Zn insulin and wild mouse
insulin in the millimolar range was investigated by measuring the
osmotic pressure at pH 7.5 in 0.1 M NaCl, 0.01 M glycine. The pH dependence
of the hexamer was studied in the pH range 6.0-8.0. At pH 6.0, 7.0 and 8.0
Zn²⁺ is present as Zn²⁺, ZnH⁺ and ZnOH⁺ respectively. The
hexamer. The hexamer is a hexamer.

72751-52-1

REFERENCES

THE UNIVERSITY OF CHICAGO

LE4 ANSWER 11 OF 20 HEALTHCARE COPYRIGHT 2000, H&H

AN 1454:025415 HCAFLIN

111:225415

TI Structural transition in the metal-free hexamer of
pH 9.5 engineered (His 64) insulin.

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

Inst. Biogen., Rheinisch-Westfäl. Tech. Hochschule, Aachen, Fed. Rep. Ger.

34. Biol. Chem. Hoppe-Seyler (1989), 370(4), 1041-45

CODEN: ECHSEI; ISSN: 0177-3493

INT JOURNAL

Figure 1. A schematic diagram of the experimental design. The subjects were divided into two groups: the control group and the experimental group. The control group received a standard training program, while the experimental group received a modified training program. The results of the training program were compared between the two groups.

For hexamer formation of native insulin the repulsive potential of 6 B13 Glu carboxylate groups coming together in the center is overcome by Zn binding to B10 His. Substitution of Gln for Glu in position B13 by site-directed mutagenesis, i.e. replacement of the repelling carboxylates by amide groups, which are offering H-bonding potential, enhances assocn. and allows a metal-free hexamer to form. Merely upon addn. of Zn ions this hexamer undergoes the TC \rightarrow IDWdrw. TFRF resp. TC \rightarrow IDWdrw. KO structural transition which in the native 2Zn insulin hexamer is inducible only by additives like inorg. anions or phenolic compds. [P13 Gln]Insulin hexamers are transformed by phenolic compds., but not by anions, even in the absence of any metal. The structural transformation of insulin can thus be brought about in 2 ways. By inorg. ions with the Zn ions as their points of attack, which preexist in the nontransformed hexamer, and by phenol, for which the binding sites close to the P5 histidines come into existence only with the transformation. Therefore transformed and nontransformed hexamers, i.e. mols. with helical and extended B chain N-terminus, must be related in a dynamic equil. Phenol acts as a wedge jamming the structure in the transformed state and trapping the Zn ions. Combination of transformed 2Zn[P13 Gln]insulin and metal-free native insulin in the absence of additives results in a redistribution of the Zn ions in favor of native insulin which is an outcome of the dynamic equil. and also demonstrates an influence of B13 charge on metal binding affinity. Transformation of a single subunit in a hexamer would lead to P8Glu \rightarrow P13Gln. It is unlikely to proceed by a concerted process involving 4 proeq. 3 mols. in 1 of the 2 layers forming the hexamer.

IT 7440-66-6, Zinc, biological studies

FL: BIO: (Biological studies)

72751-52-1

Table 1. Demographic characteristics of study population

hexamer

1. ALGERIA 1. 07. 1971 174175 11751 87 100 100

THE UNIVERSITY OF MICHIGAN

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |

II. Specific amino acid residues of the T₁ P₁ and P₂ subunits involved in the assembly hexamer

 $\lambda \in X_{\text{int}}(T)$

the cobalt ions results in dramatic changes in the visible region of the electronic spectrum and thus represents a useful spectroscopic method for studying the T to R transition. Changes in the CoL+ spectral envelope show that the aqua ligand bound with each tetrahedral CoL+ center can be replaced by SCN-, CN-, OCN-, N3- and N2-. 19F-NMR expts. show that the binding of m-trifluororesol stabilizes the R state of **zinc insulin**. The chem. shift and line broadening of the 19F singlet, which occur pre to binding, provide a useful probe of the T to R transition. Due to the appearance of new resonances in the arom. region, the 100 MHz 1H NMR spectrum of the phenol-induced R6 **hexamer** is readily distinguishable from that of the T6 form. 1H NMR studies show that phenol induces the T6 to R6 transition, both in the (GlnB13)6(Zn2+)2 **hexamer** and in the metal-free GlnB13 species. Thus, metal binding is not a prerequisite for formation of the R state in this mutant.

- IT 7440-66-6D, **Zinc, insulin hexamer complexes**
 RL: PRP (Properties)
 (conformational transitions in, spectroscopy of)
 IT 72751-52-1D, **hexamers, cobalt and zinc complexes**
 RL: PRP (Properties)
 (conformational transitions of, metal binding role in)

LE9 ANSWER 13 OF 26 HCAPLUS COPYRIGHT 2000 ACC

AN 1989:400892 HCAPLUS

DN 111:892

TI Studies on the crystal structure of Al-(L-tryptophan) insulin at 2.1 Å resolution

AU Wan, Zhuli; Liang, Dongcai

CS Inst. Biophys., Acad. Sin., Beijing, Peop. Rep. China

SO Sci. Sin., Ser. B (Engl. Ed.) (1988), 31 (2), 1440-38

CODEN: SCBSEF; ISSN: 0253-5823

DT Journal

LA English

AB In order to study the biol. effect of alterations to the N-terminus of the insulin A-chain, the crystal structure of Al-(L-Trp) insulin was detd. It was shown to belong to the trigonal system with space group R3. The parameters of the unit cell were a = b = c = 6.5 Å, a = b = c = 120°. The model was adjusted and refined by using a stereochem.-restrained least squares program, assisted by manual revision of the model based on the difference Fourier map. The final R = 0.17. The main chains of the chains of both Al-(L-Trp) residues in the asym. unit were well ordered. It was found that the Al-Trp residue of mol. I occupied two distinct positions. From the results of the three-dimensional structure it was proposed that the **zinc insulin hexameric form** is a dimer of dimer of dimer of dimer of dimer of dimer of dimer. The structural details of the insulin molecule and the structural relationship are discussed.

- IT 84134-94-1
 RL: PRP (Properties)
 (crystal structure of)

LE9 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2000 ACC

AN 1989:200449 HCAPLUS

DN 111:892

TI Dependence of insulin structure on cobalt and zinc binding

conformational transformations of porcine insulin, proinsulin, and minipreinsulin **hexamers**. Minipreinsulin is a proinsulin analog wherein the C-chain is replaced by a dipeptide crosslink between Gly-A1 and Ala-B30. A nomenclature system is proposed in which the 4-Zn and 4-Zn crystal forms of the **hexamer** are designated as the T6 and T6R3 conformations, resp. For all 3 proteins, addition of SCN⁻ reduces the rate of sequestering and removal of **zinc ion** by chelator. The effect of SCN⁻ on the rate of this process saturates at the same concn. (30 mM) known to induced the T₆-to-T_{6R3} transformation in the insulin crystal. Under both T6 and T6R3 conditions, crit. stoichiometry for high-affinity interaction between Zn²⁺ and each of the 3 proteins is shown to be 2 mol of Zn²⁺/mol of protein **hexamer**. Consequently, the finding that off-axial coordination of Zn²⁺ via His-B10 and His-B1 residues is of minor importance for the SCN⁻-induced conformational change in insulin is confirmed. Under T6 conditions, the kinetics of the reactions between insulin, proinsulin, and minipreinsulin and a variable excess of terpy are similar and biphasic. The fast phase of each reaction is 1st order in terpy and 1st order in protein-bound Zn²⁺ ($k = 0.5-1.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$) and involves the formation of a terpy-Zn²⁺-protein complex at each **zinc** sites. The slow phase of each reaction is 1st order in terpy at low concns. and tends toward a limiting, satd. value at high terpy concns. In each system, this step involves the rate-limiting dissociation of terpy-bound Zn²⁺ from the protein, followed by the rapid coordination of a 2nd terpy mol. and formation of (terpy)₂Zn²⁺. Under T6R3 conditions, the corresponding reactions for the 3 proteins are also very similar and biphasic. When compared to T6 conditions, the second-order rate const. of the fast phase is slightly reduced ($k = 0.5-0.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$). The rate of the slow phase is remarkably reduced ($k = 0.05 \text{ s}^{-1}$) and becomes zero order in terpy. The striking similarity between the kinetic parameters shows that the same process is rate-limiting for the reaction of terpy with the SCN⁻-induced form of each protein. The kinetic results indicate a mechanism where one of the two **zinc** environments per **hexamer** is transformed by SCN⁻. Thus, the slow rate obsd. under T6R3 conditions likely is limited by the rate of the SCN⁻-induced conformational change. Studies of the rate of removal of Zn²⁺ from the insulin **hexamer** under conditions similar to those which give the T6 crystal form provide further evidence consistent with these conclusions.

17 7440-66-6D, Zinc, insulin **hexamer** complexes
11062-03-6D, Proinsulin (pig), **zinc** complexes,
hexamers 12584-58-6D, Porcine insulin, **zinc**
complexes, **hexamers** 119970-48-8

AB: PKB (Properties)

(conformation of, **zinc**-binding domains in relation to)

18 ANSWER IS OF THE HAWKIN TYPE (HAWKIN) 18

AN 18-11-71 HAWKIN

IN 18-11-71

19 Insulin is a protein which is secreted by the beta cells of the pancreas.

IN 19-11-71; 19-11-71; 19-11-71; 19-11-71; 19-11-71; 19-11-71

20 19-11-71; 19-11-71; 19-11-71

21 19-11-71; 19-11-71; 19-11-71

22 19-11-71; 19-11-71; 19-11-71

23 19-11-71; 19-11-71; 19-11-71

24 19-11-71; 19-11-71; 19-11-71

25 19-11-71; 19-11-71; 19-11-71

26 19-11-71; 19-11-71; 19-11-71; 19-11-71; 19-11-71; 19-11-71

AF The title formulation contains 1.0 mg of insulin or insulin derivative, which in soln. in the physiologic pH range are predominantly present as monomers, to provide a fast absorption of the insulin administered. Des-pentapeptide (B26-30) porcine insulin-B25-amide (75 mg) was dissolved in 3 mL aq. HCl, then 5 mL of 0.02M NaH2PO4 in 1:1 phenol was added, NaOH to pH 9.5, and water to 10 mL. This 10 mL soln. was mixed with 10 mL 2 M glycylglycylcholate in 0.15M NaCl. HCl was added to pH 7.5, filled into a bottle which was sealed with a manual atomizer delivering a sp. vol. per puff, and 100 .mu.L (10 IU of insulin activity) was nasally administered through a single puff. A suppository contg. trisuccinyl human insulin, a nasal formulation contg. sulfated porcine insulin, and a nasal powder contg. des-pentapeptide (B26-30) porcine insulin-B25-amide were also formulated. Monomeric des-pentapeptide (B26-30) porcine insulin-B25-amide was absorbed faster and more reproducibly than hexameric Zn-insulin (human) by intranasal administration in rats.

hexamers and hexameric aggregates; in these units, I₁, I₂ was present as species up to and including tetramers. In other units, I₁, I₂ and I₃, monomers and dimers of I₁ appeared to be the only species present. The significance of these findings, esp. in relation to a role for I₃ in the action of insulin, is discussed.

IT 7440-66-6, biological studies

RE: BIOL (Biological study)

(insulin despot peptide analogs self-assoc. induction)

IT 55599-09-2

RE: PRP (Properties)

(self-assoc. of, divalent cation effect on)

L59 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2000 ACS

AN 1986:102026 HCAPLUS

IN 1986:1020

TI Growth of single crystals of L-Ala³⁰ pig insulin and their x-ray crystallographic analysis

AN Liu, Liwei; Chang, Xinhua; Sun, Zhili; Liang, Lianxi

CH Inst. Biophys., Acad. Sin., Beijing, 100190, P.R. China

SO Kexue Tongbao (Foreign Lang. Ed.) (1985), 30(8), 1109-11

CODEN: KHTFBU; ISSN: 0454-9847

IT Journal

LA English

AB Single crystals of [D-Ala³⁰ pig insulin (I)] [100469-14-5] were prepd. and examd. by x-ray crystallog. Crystals were grown in a buffer contg. citrate and, except for pH, optimal conditions for crystal growth were similar for those for pig insulin 2-Zn rhombohedral crystals. Isomorphism of I with 2-Zn pig insulin was very good with a difference of only 0.8 Å in C₂-axis. Results indicated that neither the mode of close packing of the hexamers of I in unit cells nor the essential conformation of the mol. was greatly changed. However, the intensities of reflections were changed and the diffraction data for I differed considerably from that of 2-Zn pig insulin. Thus, partial conformation of the I mol. was changed somewhat compared with 2-Zn pig insulin.

IT 100469-14-5

RE: PRP (Properties)

crystal structure of

L59 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2000 ACS

AN 1985:100000 HCAPLUS

IN 1985:1000

TI An application of the rotation function method to the determination of the crystal structure of (L-Met)³⁰-insulin-orientation of the molecules in the unit cell and a structural model

AN Fan, Zhili; Li, Zhili; Liang, Lianxi

CH Inst. Biophys., Acad. Sin., Beijing, 100190, P.R. China

SO Chinese Science Bulletin (Engl. Transl.) (1985), 30(10), 1109-11

CODEN: CHNSAT; ISSN: 0254-5805

IT Journal

LA Chinese

AB The value of rotation function in the crystal structure of (L-Met)³⁰-insulin [99102-79-1] using the structure of rhombohedral 2-Zn as a model was carried out. The unit cell parameters, a, b, c, which was related to the C₂ axis of a dimer, was 10.0, 10.0, 10.0 Å, respectively. The results showed that the hexamer of (L-Met)³⁰-insulin was similar to the hexamer of 2-Zn pig insulin.

Alt: ACT (Resistant)

Transition II, with zinc, penicillin in relation to

* filled

FILE 'REGISTRY' ENTERED AT 11:12:12 ON 20 DEC 2000
 USE IS SUBJECT TO THE TERMS OF YOUR STN DATA USER AGREEMENT.
 PLEASE SEE "HELP USANETTEAM" FOR DETAILS.
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STRUCTURE FILE UPDATES: 20 DEC 2000 HIGHEST RN 011-10-10-0
 DICTIONARY FILE UPDATES: 20 DEC 2000 HIGHEST RN 011-10-10-0

DATA INFORMATION NOW CURRENT THROUGH July 9, 2000

Please note that search-term pricing rules apply when
 conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT
 for details.

and 121 sqide can tot

L21 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2000 ACS
 RN 253597-48-7 REGISTRY
 CN 2: PN: US6011007 SEQID: 2 Unclaimed protein (CA) (CA INDEX NAME)
 FS PROTEIN SEQUENCE
 SQL 30
 NTE

| type | location | | | description |
|----------|----------|---|---|-------------|
| uncommon | Aaa-1 | - | - | |
| uncommon | Aaa-3 | - | - | |
| uncommon | Aaa-1 | - | - | |

SEQ 1 XVXQHLCSGH IVEALYLVCG ERGFFYTPKX
 MF Unspecified
 CI CAN
 CR CA
 LC STN Files: CA, CAPUS, TOXKIT, USSTATEFULL
 1 REFERENCES IN FILE CA (1997 TO DATE)
 1 REFERENCES IN FILE CAN (1997 TO DATE)

REFERENCE 1: 1997-01-01

L21 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2000 ACS
 RN 253597-47-6 REGISTRY
 CN 1: PN: US6011007 SEQID: 1 Unclaimed protein (CA) (CA INDEX NAME)
 FS PROTEIN SEQUENCE
 SQL 21
 NTE

1 REFERENCED IN FILE CA (1967 TO DATE)
1 REFERENCED IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 141:7-64-

no disulfide cannot be

LC ANSWER 1 OF 1: REGISTRY COPYRIGHT 1977 ADP
RN 207519-94-6 REGISTRY
CN (1A-21A), (1B-20B)-Insulin (human), 20B-[N-(1-(4-aminophenyl)-2-hydroxy-2,4-oxo-2,4-dihydro-1H-pyridin-4-yl)-L-alanyl-L-glutamyl]-L-lysine]-L-Asp (CA
INDEX NAME)
ES PROTEIN SEQUENCE
SQL 50,29,21
NTE multichain
modified (modifications were filed)

| type | ----- | location | ----- | description |
|--------|--------|----------|--------|------------------|
| bridge | Cys-2 | - | Cys-11 | disulfide bridge |
| bridge | Cys-10 | - | Cys-22 | disulfide bridge |
| bridge | Cys-6 | - | Cys-11 | disulfide bridge |

SEQ 1 FVNQHLOGGCH LVKALNIVG: ERFFFYDIE

SEQ 1 HIVEQCCTSI CPLYQLENYG H

MF CLY2 H421 R05 080 96

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, "SPATE"LL

7 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCED TO NON-SPECIFIC DERIVATIVES IN FILE CA

7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 141:1-64-

REFERENCE 2: 132:313702

REFERENCE 3: 141:1-64-

REFERENCE 4: 141:642907

REFERENCE 5: 141:1-64-

REFERENCE 6: 141:1-64-

REFERENCE 7: 141:1-64-

LC ANSWER 1 OF 1: REGISTRY COPYRIGHT 1977 ADP

RN 207519-93-5 REGISTRY

CN Insulin (human), 20B-[N-(1-(4-aminophenyl)-2-hydroxy-2,4-oxo-2,4-dihydro-1H-pyridin-4-yl)-L-alanyl-L-glutamyl]-L-lysine]-L-Asp (CA INDEX NAME)

ES PROTEIN SEQUENCE

SQL 51,30,21

SEQ 1 EVNQHLCQSH LVEALYLKCKS ERGFFYTHKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C281 H421 N65 O61 S6

CI MAN

SR CA

LN CTH File: CA, VALLIS, TALLIT, CHATFIELD

1 REFERENCED IN FILE CA (1967 TO DATE)

1 REFERENCED TO NON-SPECIFIC DERIVATIVES IN FILE CA

1 REFERENCED IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 110:1436

LN ANSWER 4 OF 12 REGISTRY COPYRIGHT 1974 AND

RN 207519-92-4 REGISTRY

CN Insulin (human), 29R-[Nc-[(3.alpha.,5.beta.,12.alpha.)-3,12-dihydroxy-24-oxocholan-24-yl]-L-lysine]- (2CI) (CA INDEX NAME)

PR PROTEIN SEQUENCE

SQL 51,30,21

NTE multichain.

modified (modifications unspecified)

| TYPE | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 EVNQHLCQSH LVEALYLKCKS ERGFFYTHKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C281 H421 N65 O80 S6

CI MAN

SR CA

LN CTH File: CA, VALLIS, TALLIT, CHATFIELD

1 REFERENCED IN FILE CA (1967 TO DATE)

1 REFERENCES IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 124:1374

LN ANSWER 4 OF 53 REGISTRY COPYRIGHT 1974 AND

RN 207519-90-2 REGISTRY

CN Insulin (human), 29R-[Nc-[(3.alpha.,5.beta.,12.alpha.)-3,12-dihydroxy-24-oxocholan-24-yl]-L-lysine]- (2CI) (CA INDEX NAME)

PR PROTEIN SEQUENCE

SQL 51,30,21

NTE multichain.

modified (modifications unspecified)

| TYPE | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | Disulfide bridge |
| bridge | Cys-19 - Cys-20' | Disulfide bridge |
| bridge | Cys-6' - Cys-11' | Disulfide bridge |

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1028

LC0 ANSWER 5 OF 53 REGISTRY COPYRIGHT 2000 ACS
RN 207519-89-9 REGISTRY
CN Insulin (human), Lys-[N6-[4-[2-[(1-carboxy-2-(acetylamino)ethoxy]-1,4-dioxobutyl]-L-lysine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
SQL 51,30,21
NTE multichain
modified (modifications unspecified)

| type | location | description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 FGNQHLGGSH LNEALYLVOG ERGFFFTPKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C279 H422 N66 Q82 S6

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USFATEFULL

1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1028

LC0 ANSWER 6 OF 53 REGISTRY COPYRIGHT 2000 ACS
RN 207519-88-8 REGISTRY
CN Insulin (human), Lys-[N6-[4-[2-[(1-carboxy-2-(acetylamino)ethoxy]-1,4-dioxobutyl]-L-lysine]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
SQL 51,30,21
NTE multichain
modified (modifications unspecified)

| type | location | description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 FGNQHLGGSH LNEALYLVOG ERGFFFTPKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C279 H422 N66 Q82 S6

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USFATEFULL

CN Insulin (human), 29B-[N6-(4-benzoyl-L-phenylalanyl)-L-lysine]- (9'1) (CA INDEX NAME)
 FS PROTEIN SEQUENCE
 SQL 51,30,21
 NTE multichain
 modified (modifications unspecified)

| Type | Location | Description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 EVNQHLCQSH LVEALYLVCG ERGFFYTPKT

SEQ 1 GIVEQCCTSI CSNYHLENYE N

MF C275 H414 N66 O81 S6

CI MAN

CR CA

LC CTN Files: CA, CAPUS, T-XLIT, UNATEFULL
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1 REFERENCES IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 129:1026

LOG ANSWER 8 OF 53 REGISTRY COPYRIGHT 2000 ACS

RN 207519-85-5 REGISTRY

CN Insulin (human), 29B-[N6-(4-benzoyl-L-phenylalanyl)-L-lysine]- (9'1) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SQL 51,30,21

NTE multichain

modified (modifications unspecified)

| Type | Location | Description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 EVNQHLCQSH LVEALYLVCG ERGFFYTPKT

SEQ 1 GIVEQCCTSI CSNYHLENYE N

MF C275 H414 N66 O81 S6

CI MAN

CR CA

LC CTN Files: CA, CAPUS, T-XLIT, UNATEFULL
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 129:1026

LOG ANSWER 8 OF 53 REGISTRY COPYRIGHT 2000 ACS

RN 207519-84-4 REGISTRY

CN Insulin (human), 29B-[N6-(4-benzoyl-L-phenylalanyl)-L-lysine]- (9'1) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SQL 51,30,21

NTE multichain

modified (modifications unspecified)

| Type | Location | Description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

| | | | | |
|--------|--------|---|--------|------------------|
| bridge | Cys-7 | - | Cys-21 | disulfide bridge |
| bridge | Cys-19 | - | Cys-21 | disulfide bridge |
| bridge | Cys-6 | - | Cys-11 | disulfide bridge |

SEQ 1 FVNQHLCGSH LNEALYLVOG ERGFYTPK

SEQ 1 GIVEQCTSI CILYALENY N

MF C122 H4 9 D1 074 10

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOLIT, UNDATELL

1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1026

LOC ANSWER 10 OF 58 REGISTRY COPYRIGHT 2000 AM

RN 207519-83-3 REGISTRY

CN Insulin (human), 29k-[N6-(1-oxododecyl)-L-lysine]- (901) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SOL 51,30,21

NTE multichain

modified (modifications unspecified)

| type | ----- | location | ----- | description |
|--------|--------|----------|--------|------------------|
| bridge | Cys-7 | - | Cys-21 | disulfide bridge |
| bridge | Cys-19 | - | Cys-21 | disulfide bridge |
| bridge | Cys-6 | - | Cys-11 | disulfide bridge |

SEQ 1 FVNQHLCGSH LNEALYLVOG ERGFYTPK

SEQ 1 GIVEQCTSI CILYALENY N

TE 129:11-1

MF C122 H4 9 D1 074 10

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOLIT, UNDATELL

1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1026

REFERENCE 2: 129:1026

REFERENCE 3: 129:1026

REFERENCE 4: 129:1026

LOC ANSWER 11 OF 58 REGISTRY COPYRIGHT 2000 AM

RN 207519-82-2 REGISTRY

CN Insulin (human), 29k-[N6-(1-oxododecyl)-L-lysine]- (901) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SOL 51,30,21

NTE multichain

modified (modifications unspecified)

bridge Cys-6' - Cys-11' Disulfide bridge

SEQ 1 FVNQHLCGSH LVEALYLVCG ERGFFYTHKT

SEQ 1 GIVEQCCCTSI CELYOLENYT N

MF C166 H451 N61 O76 S9

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXKIT, USHATFALL

1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1028

LOC ANSWER 11 OF 58 REGISTRY COPYRIGHT 2000 ACP

RN 207519-80-0 REGISTRY

CH Insulin (human), 298-[N-(4-cyclohexyl)-1-oxopropyl]-L-cysteine]-[C1] (CA INDEX NAME)

PS PROTEIN SEQUENCE

COL 51,30,21

MTX multichain

modified (modifications unspecified)

| type | ----- | location | ----- | Description |
|--------|--------|----------|---------|------------------|
| bridge | Cys-7 | - | Cys-7' | Disulfide bridge |
| bridge | Cys-19 | - | Cys-20' | Disulfide bridge |
| bridge | Cys-6' | - | Cys-11' | Disulfide bridge |

SEQ 1 FVNQHLCGSH LVEALYLVCG ERGFFYTHKT

SEQ 1 GIVEQCCCTSI CELYOLENYT N

MF C166 H547 N65 O76 S6

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXKIT, USHATFALL

1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1028

LOC ANSWER 12 OF 58 REGISTRY COPYRIGHT 2000 ACP

RN 207519-79-7 REGISTRY

CH Insulin (human), 198-[N-(4-cyclohexyl)-1-oxopropyl]-L-cysteine]-[C1] (CA INDEX NAME)

PS PROTEIN SEQUENCE

COL 51,30,21

MTX multichain

modified (modifications unspecified)

| type | ----- | location | ----- | Description |
|--------|--------|----------|---------|------------------|
| bridge | Cys-7 | - | Cys-7' | Disulfide bridge |
| bridge | Cys-19 | - | Cys-20' | Disulfide bridge |

CA
 STN Files: CA, CAPLUS, TMLIT, CHATEAU
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1128

LC ANSWER 14 OF 1: REGISTRY COPYRIGHT 1967 AM
 RN 207519-78-6 REGISTRY
 CN Insulin (human), 29B-[N-(cyclohexylacetyl)-L-lysine]- (411) (CA INDEX NAME)
 EC PROTEIN SEQUENCE
 SQL 51,30,21
 NTE multichain
 modified (modifications unspecified)

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-19' | disulfide bridge |
| bridge | Cys-11 - Cys-11' | disulfide bridge |

SEQ 1 FUNHLOCH LWEALYLVO ERGFFYTHI

SEQ 1 GIVEQCTGT CULYOLENY H

MF C265 H495 N65 Q78 L36

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TMLIT, CHATEAU
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1026

LC ANSWER 14 OF 1: REGISTRY COPYRIGHT 1967 AM
 RN 186003-66-7 REGISTRY
 CN Insulin (human), 29B-[N-(1-oxohexadecyl)-L-lysine]- (401) (CA INDEX NAME)
 EC PROTEIN SEQUENCE
 SQL 51,30,21
 NTE multichain
 modified (modifications unspecified)

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-19' | disulfide bridge |
| bridge | Cys-11 - Cys-11' | disulfide bridge |

SEQ 1 FUNHLOCH LWEALYLVO ERGFFYTHI

SEQ 1 GIVEQCTGT CULYOLENY H

MF C265 H495 N65 Q78 L36

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TMLIT, CHATEAU
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:1026

REFERENCE 1: 150:101-
 REFERENCE 2: 150:103-11
 REFERENCE 3: 150:104-11
 REFERENCE 4: 150:105-12
 REFERENCE 5: 150:106-16
 REFERENCE 6: 150:107-19
 REFERENCE 7: 150:108-20
 REFERENCE 8: 150:109-21
 REFERENCE 9: 150:110-22
 REFERENCE 10: 150:111-23

LC0 ANSWER 16 OF 17 REGISTRY COPYRIGHT 1980 AD
 EN 175895-36-0 REGISTRY
 CM Insulin (human), 2BB-[N6-(1-oxotetrad-2-yl-L-lysine)- C61] (CA INDEX
 NAME)
 FS PROTEIN SEQUENCE
 SQL 51,30,21
 NTE multichain
 modified (modifications unspecified)

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 SWISSPROT SEQUENCE OF HEPATITIS

SR 1 GIVEWORTHY POLYMERASE
 DR 270588-46-0
 MF C271 H409 N65 O78 S
 CI 1000
 SR CA
 LC STM Files: CA, CAPUS, TOXLIB, USEPATELL
 1 REFERENCES IN FILE CA 1100 1101
 1 REFERENCES IN FILE CA 1100 1102
 1 REFERENCES IN FILE CA 1100 1103

REFERENCE 1: 150:101-
 REFERENCE 2: 150:103-11
 REFERENCE 3: 150:104-11
 REFERENCE 4: 150:105-12
 REFERENCE 5: 150:106-16
 REFERENCE 6: 150:107-19
 REFERENCE 7: 150:108-20
 REFERENCE 8: 150:109-21
 REFERENCE 9: 150:110-22
 REFERENCE 10: 150:111-23

REFERENCE 1: 1241107

10 ANSWER 17 OF 53 REGISTRY COPYRIGHT 1997 AND
 EN 169535-38-0 REGISTRY
 CN 1-9-peptide (synthetic 5-amino acid extension) fusion protein with
 alpha-factor receptor (Saccharomyces cerevisiae leader peptide) fusion
 protein with peptide (synthetic 5-amino acid) fusion protein with insulin
 B-chain [1-arginine, 1-arginine] (human) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 19: PN: US6011007 SEQID: 45 claimed protein

FS PROTEIN SEQUENCE

SQL 146

SEQ 1 MRFFSIFTAV LFAASSALAA PNTTTEDET AQIPAEAVIG YQPLENFEV
 51 AVLPFSNSTN NGLLPINTTI ASIAAKEEGV SMAKKEEAEA EAKPEYDHLG
 101 GSHLVEALYI VYGERGEYF INTEGIVEG STYDGLYI EYDGLY

MF Unspecified

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, UNPATEFULL
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 12273642

REFERENCE 2: 123322102

100 ANSWER 18 OF 53 REGISTRY COPYRIGHT 1997 AND

EN 169535-36-8 REGISTRY

CN 1-6-Peptide (synthetic) fusion protein with alpha-factor receptor
 (Saccharomyces cerevisiae leader peptide) fusion protein with peptide
 (synthetic 5-amino acid) fusion protein with insulin B-chain [1-arginine]
 (human) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 21: PN: US6011007 SEQID: 48 claimed protein

FS PROTEIN SEQUENCE

SQL 145

SEQ 1 MRFFSIFTAV LFAASSALAA PNTTTEDET AQIPAEAVIG YQPLEGDFV
 51 AVLPFSNSTN NGLLPINTTI ASIAAKEEGV SMAKKEEAEA EAKPEYDHLG
 101 GSHLVEALYI VYGERGEYF INTEGIVEG STYDGLYI EYDGLY

MF Unspecified

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, UNPATEFULL
 1 REFERENCES IN FILE CA (1967 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 12273642

REFERENCE 2: 123322102

100 ANSWER 19 OF 53 REGISTRY COPYRIGHT 1997 AND

EN 169535-34-6 REGISTRY

CN 1-6-Peptide (synthetic) fusion protein with alpha-factor receptor
 (Saccharomyces cerevisiae leader peptide) fusion protein with peptide
 (synthetic 5-amino acid) fusion protein with insulin B-chain [1-arginine]
 (human) (9CI) (CA INDEX NAME)

MF Unspecified

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USPATEFULL
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 123:322102

L60 ANSWER 20 OF 53 REGISTRY COPYRIGHT 2000 ACP

RN 169535-32-4 REGISTRY

EN Receptor, .alpha.-factor (Saccharomyces cerevisiae leader peptide) fusion protein with peptide (synthetic 5-amino acid) fusion protein with insulin B-chain [3-arginine] (human) (2011) (CA INDEX NAME)

OTHER NAMES:

EN 11: EN: UC0011007 SEQID: 34 claimed protein

FS PROTEIN SEQUENCE

SQL 137

SEQ 1 MSFDSIFTAV LFAASSALAA PNTTTEDET AIPAEAVD YELAEDEFV
51 AVLI FSHSTH NMLFSTTH ASIAAREETV SAREETVNH D'GRLAL
101 YIVGGERGEF YTIKTEGIVE QNTSLCLLY QLENVNH

MF Unspecified

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USPATEFULL
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 123:322102

L60 ANSWER 21 OF 53 REGISTRY COPYRIGHT 2000 ACP

RN 169535-30-2 REGISTRY

EN Peptide (Saccharomyces cerevisiae synthetic signal peptide) fusion protein with peptide (synthetic 5-amino acid) fusion protein with insulin (human A-chain) fusion protein with insulin (human plus B-chain) (2011) (CA INDEX NAME)

OTHER NAMES:

EN 11: EN: UC0011007 SEQID: 35 claimed protein

FS PROTEIN SEQUENCE

SQL 102

SEQ 1 MSFDSIFTAV LFAASSALAA PNTTTEDET AIPAEAVD YELAEDEFV
51 AVLI FSHSTH NMLFSTTH ASIAAREETV SAREETVNH D'GRLAL
101 YIVGGERGEF YTIKTEGIVE QNTSLCLLY QLENVNH

MF Unspecified

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USPATEFULL
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 123:322102

140

IC STN Files: CA, CHAIRS, TOLKIT, WHATFILL
2 REFERENCES IN FILE CA (LAST 2 PAGES)
1 REFERENCES IN FILE CHAIRS (LAST 2 PAGES)

REFERENCE 2: 143:522102

104

10 CTN FILE#1 CA, CHEN, TUNG, CHIAHUI
2 REFERENCES IN FILE CA 1967 TO DATE
2 REFERENCES IN FILE CHEN (1967 TO DATE)

REFERENCE 1. *Ann. N.Y. Acad. Sci.* 1974; 274: 1-10.

104

bridge Cys-14 - Cys-21' disulfide bridge
bridge Cys-6' - Cys-11' disulfide bridge

SEQ 1 FVNQHLCGSH LVEALYLVCS ERGFFYTKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C286 H428 N66 O81 S6

CI MAN

SR CA

LC STN Files: CA, CAPLIN, TOXLIT, UNFAITHFUL
2 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLIN (1967 TO DATE)

REFERENCE 1: 12:174645

REFERENCE 2: 12:1722108

Leo ANSWER 32 OF 53 REGISTRY COPYRIGHT 1968 ACS

RN 169148-72-5 REGISTRY

CN Insulin (human), 29H-[Nc-[(2.alpha.,5.beta.)-5-hydroxy-24-oxochoiran-24-yl]-L-lysine]- (PCI) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SQL 51,30,21

NTE multichain

modified (modifications unspecified)

| type | location | description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 FVNQHLCGSH LVEALYLVCS ERGFFYTKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C281 H421 N66 O79 S6

CI MAN

SR CA

LC STN Files: CA, CAPLIN, TOXLIT, UNFAITHFUL
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2 REFERENCES IN FILE CAPLIN (1967 TO DATE)

REFERENCE 1: 12:174645

REFERENCE 2: 12:1722108

REFERENCE 3: 12:1722108

Leo ANSWER 33 OF 53 REGISTRY COPYRIGHT 1968 ACS

RN 169148-71-4 REGISTRY

CN Insulin (human), 14H-[Nc-[(2.alpha.)-2-hydroxy-24-oxochoiran-24-yl]-L-lysine]- (PCI) (CA INDEX NAME)

FS PROTEIN SEQUENCE

SQL 51,30,21

SEQ 1 FVNQHLOGSH LVEALYLVCG ERGFFVYTKT

SEQ 1 GIVEQCTSI CGLYPLENY: N

MF 0250 H404 14 NOV 076 36

CI MAN

SE CA

LC STN Files: CA, CAPUS, TOXLIT, USPTFULL
1 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 132:73(48)

REFERENCE 2: 173:322102

LOG ANSWER 34 OF 53 REGISTRY COPYRIGHT 2000 AM

RN 169148-70-3 REGISTRY

IN Insulin (human), 23B-[Nc-[D-]-[D-]-carboxy-L-oxopropylamino]-ethoxy]-L-oxohexadecyl]-L-lysine]- (9'1) (CA INDEX NAME)

FS PROTEIN SEQUENCE

QL 51,30,21

NTE multichain

modified (modifications unspecified)

| type | ----- | location | ----- | Description |
|--------|--------|----------|---------|------------------|
| bridge | Cys-7 | - | Cys-7' | disulfide bridge |
| bridge | Cys-19 | - | Cys-20' | disulfide bridge |
| bridge | Cys-6' | - | Cys-11' | disulfide bridge |

SEQ 1 FVNQHLOGSH LVEALYLVCG ERGFFVYTKT

SEQ 1 GIVEQCTSI CGLYPLENY: N

MF 0279 H422 NOV 082 36

CI MAN

SE CA

LC STN Files: CA, CAPUS, TOXLIT, USPTFULL
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 173:322102

LOG ANSWER 34 OF 53 REGISTRY COPYRIGHT 2000 AM

RN 169148-69-0 REGISTRY

IN Insulin (human), 23B-[Nc-[D-]-[D-]-carboxy-L-oxopropylamino]-ethoxy]-L-oxohexadecyl]-L-lysine]- (9'1) (CA INDEX NAME)

FS PROTEIN SEQUENCE

QL 51,30,21

NTE multichain

modified (modifications unspecified)

| type | ----- | location | ----- | Description |
|------|-------|----------|-------|-------------|
|------|-------|----------|-------|-------------|

| Type | ----- Interval ----- | Sub-interval |
|----------|------------------------|----------------------------|
| Finite | $\text{Type} = \infty$ | $\text{Interval} = \infty$ |
| Infinite | $\text{Type} = 0$ | $\text{Interval} = \infty$ |
| Finite | $\text{Type} = 0$ | $\text{Interval} = 0$ |

3 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 123:322102

LOC ANSWER 39 OF 53 REFLECTED COMBINED WITH ANSW
RN 169148-66-7 REFLECTED
CN Insulin (human), 29B-[N6-[4-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodophenyl]acetyl]-L-lysine]- (901) (CA INDEX NAME)
FS PROTEIN SEQUENCE
CPL 50,29,21
NTE multichain
modified (modifications unspecified)

| type | ----- | location | ----- | description |
|--------|-------|----------|-----------|------------------|
| bridge | | Cys-7 | - Cys-7' | disulfide bridge |
| bridge | | Cys-19 | - Cys-20' | disulfide bridge |
| bridge | | Cys-6' | - Cys-11' | disulfide bridge |

SEQ 1 FVNQHLOCSH LVEALYLVWG ERGFFYYTK

SEQ 1 GIVEQCCTSI CGLYQLENYC N

MF C272 H392 I4 N66 O40 S6

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, UNFATEFUL
3 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 123:322102

REFERENCE 3: 123:322102

LOC ANSWER 39 OF 53 REFLECTED COMBINED WITH ANSW
RN 169148-65-6 REFLECTED
CN Insulin (human), 29B-[N6-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]acetyl]-L-lysine]- (901) (CA INDEX NAME)
FS PROTEIN SEQUENCE
CPL 50,29,21
NTE multichain
modified (modifications unspecified)

| type | ----- | location | ----- | description |
|--------|-------|----------|-----------|------------------|
| bridge | | Cys-7 | - Cys-7' | disulfide bridge |
| bridge | | Cys-19 | - Cys-20' | disulfide bridge |
| bridge | | Cys-6' | - Cys-11' | disulfide bridge |

SEQ 1 FVNQHLOCSH LVEALYLVWG ERGFFYYTK

SEQ 1 GIVEQCCTSI CGLYQLENYC N

MF C272 H392 I4 N66 O40 S6

CI MAN

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, UNFATEFUL
3 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

RECEIVED: 11/1/93

[illegible]

| type | location | description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-10 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

11 REFERENCES IN FILE CIELUS (1967 TO DATE)

[illegible]

169148-63-4

7 REFERENCES IN FILE CA (1967 TO DATE)

REFERENCE 1: 131:35648
 REFERENCE 2: 131:341993
 REFERENCE 3: 130:325400
 REFERENCE 4: 139:1025
 REFERENCE 5: 125:138815
 REFERENCE 6: 124:127039
 REFERENCE 7: 124:121132

160 ANSWER 43 OF 53 REGISTRY COPYRIGHT 2000 ACP
 RN 169148-61-2 REGISTRY
 CN Insulin (human), NA-[(1,1-dimethylethoxy)carbonyl]-NH-[(1,1-dimethylethoxy)carbonyl]- (901) CA INDEX NAME
 FS PROTEIN SEQUENCE
 SQL 50,29,21
 NTE multichain
 modified (modifications unspecified)

| type | location | description |
|--------|------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-19' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 FVNQHLCGSH LVEALYLVCG ERGFFFTPK

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF 1067 H300 N45 081 35

SI 1000

SR CA

LC STN Files: CA, CAPLUS, TOXLIT, USEPATFULL

2 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCED TO NCI-DEP (NCI) RESEARCH IN FILE CA

2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:35648

REFERENCE 2: 131:341993

160 ANSWER 44 OF 53 REGISTRY COPYRIGHT 2000 ACP
 RN 169148-60-1 REGISTRY
 CN Insulin (human), NA-[(1,1-dimethylethoxy)carbonyl]-NH-[(1,1-dimethylethoxy)carbonyl]- (901) CA INDEX NAME
 FS PROTEIN SEQUENCE
 SQL 50,29,21
 NTE multichain
 modified (modifications unspecified)

A LETTERHEAD IN BLUE INK. 1947-50.

4 REFERENCE: IN FILE "RENT" (44-38861)

REFERENCE 4: 123:322102

NTE multichain

modified (modifications unspecified)

| type | ----- | location | ----- | description |
|--------|--------|----------|---------|------------------|
| bridge | Cys-7 | - | Cys-7' | disulfide bridge |
| bridge | Cys-19 | - | Cys-20' | disulfide bridge |
| bridge | Cys-6' | - | Cys-11' | disulfide bridge |

SEC 1 FVNDJLGGSH LYEALYLVCS BRGEFYTEK

DATE: APR 21 1964; TO: CARLOS, TORRES, MONTAÑANA

3 REFERENCES IN FILE CAPLIS (1967 TO DATE)

[illegible]

50, 29, 21

REFERENCE 1: 111:7364a
REFERENCE 2: 120:102b
REFERENCE 3: 122:114-115
REFERENCE 4: 125:15-16
REFERENCE 5: 124:127-129
REFERENCE 6: 123:32-102

```
LN# ANSWER #1 OF IS REGISTRY KEYRIGHT 100 AM
PN 169148-57-6 REGISTRY
CN (1A-21A), (1B-29B)-Insulin (human), NHB-[N-(L-alpha-amino acid)-L-lysine]- (CA INDEX NAME)
ES PROTEIN SEQUENCE
SQL 50,29,21
NTE multichain
modified (modifications unspecified)
```

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-19' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

[illegible]

| | | | | |
|--------|--------|---|--------|------------------|
| bridge | Cys-1 | - | Cys-11 | disulfide bridge |
| bridge | Cys-19 | - | Cys-11 | disulfide bridge |
| bridge | Cys-6 | - | Cys-11 | disulfide bridge |

SEQ 1 FVNQHLOGSH LNEALYLNGS ERGEFFYTER

SE 1 GIVEQCTSI CSNYOLENYC N

MF 0264 H387 N65 078 36

CI MAN

SR CA

LC STN Files: CA, CARLOS, TOXMIT, UNPATEMIL

* REFERENCED IN FILE CA 10 1 1 DATE

* REFERENCED TO NON-SPECIFIC DERIVATIVES IN FILE CA

* REFERENCED IN FILE CARLOS (1960 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 129:1028

REFERENCE 3: 129:12112

L60 ANSWER 49 OF 53 REGISTRY COPYRIGHT 1990 AUC

RN 169148-55-4 REGISTRY

CN (1A-21A), (1B-29B)-Insulin (human), 29B-(N6-(1-octadecyl)-L-lysine)- (901)
(CA INDEX NAME)

ES PROTEIN SEQUENCE

SQL 50,29,21

NTE multichain

modified (modifications unspecified)

| type | location | Description |
|--------|-----------------|------------------|
| bridge | Cys-1 - Cys-11 | disulfide bridge |
| bridge | Cys-19 - Cys-11 | disulfide bridge |
| bridge | Cys-6 - Cys-11 | disulfide bridge |

SEQ 1 FVNQHLOGSH LNEALYLNGS ERGEFFYTER

SEQ 1 GIVEQCTSI CSNYOLENYC N

MF 0263 H394 N64 076 36

CI MAN

SR CA

LC STN Files: CA, CARLOS, TOXMIT, UNPATEMIL

* REFERENCED IN FILE CA 10 1 1 DATE

* REFERENCED TO NON-SPECIFIC DERIVATIVES IN FILE CA

* REFERENCED IN FILE CARLOS (1960 TO DATE)

REFERENCE 1: 132:73648

REFERENCE 2: 129:1028

REFERENCE 3: 129:12112

REFERENCE 4: 129:12112

SQL 51,30,21
NTE multichain

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-21 | disulfide bridge |
| bridge | Cys-19 - Cys-20 | disulfide bridge |
| bridge | Cys-6 - Cys-11 | disulfide bridge |

SEQ 1 EVNHQHL/GSH LVEALYLYCT ERGFFYYTHKT

SEQ 1 GIVEQOOTSI CALYALENYE N

MF CL6% H*89 N6% G7% S6

CI MAN

CR CA

LC STN Files: CA, CALUS, CASREACT, FOXLIT, UNHATFULL
* REFERENCES IN FILE CA (1967 TO DATE)
* REFERENCES IN FILE CALUS (1967 TO DATE)

REFERENCE 1: 120:1006

REFERENCE 2: 120:2444-4

REFERENCE 3: 121:222192

RCG ANSWER 51 OF 53 REGISTRY COPYRIGHT LINE A13

RN 120177-51-7 REGISTRY

CN Insulin (attle), NA-[(1,1-dimethylethoxy)carbonyl]-αA-L-threonine-1αA-L-
isoleucine-29B-[N6-[(1,1-dimethylethoxy)carbonyl]-L-lysine]-αB-α-L-
alanine- (901) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 3,4,44,45,90,91-Hexathia-,11,14,17,21,23,26,29,33,35,38,41,44,51,54,57,,6
,63,66,69,72,75,78,81,84,86-hexaazabicyclo[7.11.7]3-nonacontane,
cyclic peptide deriv.

CN Insulin (ox), NA-[(1,1-dimethylethoxy)carbonyl]-αA-L-threonine-1 A-L-
L-L-lysine-αB-[N6-[(1,1-dimethylethoxy)carbonyl]-L-lysine]-αB-α-L-
alanine-

FS PROTEIN SEQUENCE

SQL 50,29,21

NTE multichain

contains 6 disulfide bridges

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-21 | disulfide bridge |
| bridge | Cys-19 - Cys-20 | disulfide bridge |
| bridge | Cys-6 - Cys-11 | disulfide bridge |

SEQ 1 EVNHQHL/GSH LVEALYLYCT ERGFFYYTHKT

SEQ 1 GIVEQOOTSI CALYALENYE N

MF CL6% H*89 N6% G7% S6

CI MAN

CR CA

LC STN Files: CA, CALUS, CASREACT, FOXLIT, UNHATFULL

CN 1A-1A, 1B-2B -Insulin (human) (PDI) (A INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 1,4,44,45,46,51-Bovine-1,11,14,17,20,23,26,27,31,34,37,41,44,47,51,54,57,61,71,74,77,81,84,87-threo-threosyl-Lys(20,11,71) in bovine, cyclic peptide deriv.
 CN Insulin (ox), 8A-L-threonine-1(A-L-isoleucine-3B-B-L-alanine-
 OTHER NAMES:
 CN Des-alanine-(B30)-insulin (p-rodin)
 CN Des(B-43-alanine)-p-rodin
 CN Des(B30)-insulin (human)
 CN Des-B30-alanine-insulin (p-rodin)
 CN Des-alanine-(B30)-p-rodin-insulin
 EC PROTEIN SEQUENCE
 Sgl. 50,29,21
 NTE multi-chain.

| type | ----- location ----- | description |
|--------|----------------------|------------------|
| bridge | Cys-7 - Cys-7' | disulfide bridge |
| bridge | Cys-19 - Cys-20' | disulfide bridge |
| bridge | Cys-6' - Cys-11' | disulfide bridge |

SEQ 1 FVNQHLCGSH LVEALYLVCG ERGFFFTPK

SEQ 1 GIVEQCCTSI CSLYQLENYC N

DR 121796-35-8, 130587-81-4, 122022-05-1, 10-637-86-4, 7672-42-3,
 74870-05-6, 78642-50-3, 144637-10-1, 80155-09-6, 81054-09-1, 84860-7 -1,
 282528-78-3, 289054-43-9

MF C253 H376 N64 O75 SC

CI MAN

LC STN Files: CA, CAPUS, CASREACT, MEDLINE, TWOLIT, UNIPATELL
 87 REFERENCES IN FILE CA (1967 TO DATE)
 4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 87 REFERENCES IN FILE TWOLIT (1967 TO DATE)

REFERENCE 1: 133:1367

REFERENCE 2: 133:99679

REFERENCE 3: 131:3273

REFERENCE 4: 131:63454

REFERENCE 5: 131:3294

REFERENCE 6: 131:1118

REFERENCE 7: 131:1118

REFERENCE 8: 131:1118

REFERENCE 9: 131:1118

REFERENCE 10: 131:1118

LC 131:1118 131:1118 131:1118 131:1118 131:1118

LC 131:1118 131:1118

CN Human insulin
 CN Humulin
 CN Humulin R
 CN Insulin (Cercopithecus aethiops)
 CN Insulin (Macaca fascicularis)
 CN Insulin (Macaca mulatta)
 CN Insulin (Pan troglodytes)
 CN L-Threonine, L-phenylalanyl-L-valyl-L-asparaginyl-L-glutaminyl-L-histidyl-L-leucyl-L-cysteinylglycyl-L-seryl-L-histidyl-L-leucyl-L-valyl-L-alpha.-glutamyl-L-alanyl-L-leucyl-L-tyrosyl-L-leucyl-L-valyl-L-cysteinylglycyl-L-alpha.-glutamyl-L-arginylglycyl-L-phenylalanyl-L-phenylalanyl-L-tyrosyl-L-threonyl-L-prolyl-L-lysyl-, cyclic ('.fwdarw.'), ('.fwdarw.')-bis(disulfide) with glycyl-L-isoleucyl-L-valyl-L-alpha.-glutamyl-L-glutaminyl-L-cysteinyl-L-cysteinyl-L-threonyl-L-seryl-L-isoleucyl-L-cysteinyl-L-seryl-L-leucyl-L-tyrosyl-L-glutaminyl-L-leucyl-L-alpha.-glutamyl-L-asparaginyl-L-tyrosyl-L-cysteinyl-L-asparagine-cyclic ('.fwdarw.')-disulfide
 CN Novolin R
 CN Penfil R
 CN Ultraphane
 FS PROTEIN SEQUENCE
 SQL 51,30,21
 NTE multichain

| type | ----- | location | ----- | Description |
|--------|--------|----------|---------|------------------|
| bridge | Cys-7 | - | Cys-7' | disulfide bridge |
| bridge | Cys-19 | - | Cys-20' | disulfide bridge |
| bridge | Cys-6' | - | Cys-11' | disulfide bridge |

SEQ 1 FVNQHLCGSH LVEALYLVCG ERGFEYTPKT

SEQ 1 GIVEQCCTSI CSLYQLENYC N

MF C857 H363 N65 OTT 26

CI COM, MAN

LC STN Files: AGRICOLA, ARLINE, AMARSTR, BIOBISINESS, BIOGIC, BISTENEN,
 TA, CARFRUIT, CARLIS, CACREACT, CERN, CEN, CHERCATS, CHEMLIST, CIN,
 CSCHER, DDFU, BIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
 IFICDB, IFIPAT, IFIUP, INSIDIRECTORY, IFA, MEDLINE, MROK, PROMT,
 STEEP, TAYLOR, T XLT, WMAN, WHEATON, ZEP
 (*file contains numerically searchable property data)

Other Sources: EINECS, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

478 REFERENCES IN FILE TA 1000000000

479 REFERENCES TO NON-CHEMLIST LITERATURE IN FILE TA

480 REFERENCES IN FILE TAYLOR 1000000000

REFERENCE 1: 1000000000

REFERENCE 2: 1000000000

REFERENCE 3: 1000000000

REFERENCE 4: 1000000000

REFERENCE 5: 1000000000

→ 4.16.19.19

RM: 23713-49-7 REGISTRY

7-10-68
7-10-68

OTHER NAMES:

CN Zinc cation

(U) Zinc di-oxide

ZN Zinc divalent ion

237 *John S. G. Jones*

21. Zingales, L. (1995).

Zinc (24)

CN Zinc (II)

```

ON      LINE(11)
ON      LINE(11)  OUT:ON

```

CN Zinc(II) ion

$$\text{CN}^- + \text{Zn}^{2+} \rightarrow \text{Zn(CN)}_4^{2-}$$

MF Zn

10 STN File-s: AGRICOLA, ANABSTR, BIZBUSINESS, BIOGLO, BIOTECHNO, CA,
11 CARLIN, CASREACT, GEN, GIN, HEP, IATHEANA, IMMUN, KIDASH, LEITER,
12 LEIPAT, LEUDR, NIGHTIC, PIRA, PROMT, TOWLINE, TOXLOT, UNPATEFUL, VET
13 (*File contains numerically searchable property data)

 $2:1$

6674 REFERENCES IN FILE CA (1967 TO DATE)

179 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE 66

3090 REFERENCES IN FILE CAPIUS (1967 TO DATE)

REFERENCE 1: 254:10269

THE UNIVERSITY OF CHICAGO PRESS

REFERENCE 3: 134:10035

[illegible]

REFERENCE 1: 133:167479

$\frac{1}{\sqrt{\pi}} \int_{-\infty}^{\infty} f(x) \delta(x-a) dx = f(a)$

$\begin{array}{ccccccc} \text{H} & \text{O} & \text{C} & \text{N} & \text{S} & \text{P} & \text{Cl} \\ \text{H}_2\text{O} & \text{CO}_2 & \text{SO}_2 & \text{NO}_2 & \text{PO}_4 & \text{HCl} & \text{HBr} \end{array}$

[illegible][illegible][illegible]

Zn

124447 REFERENCES IN FILE CA 1000 TO DATE
10306 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
124448 REFERENCES IN FILE CA1000 TO DATE
124449 REFERENCES IN FILE CA 1000 TO DATE

| | | |
|-----------|-----|-----------|
| REFERENCE | 1: | 184:10857 |
| REFERENCE | 2: | 184:10858 |
| REFERENCE | 3: | 184:10859 |
| REFERENCE | 4: | 184:10860 |
| REFERENCE | 5: | 184:10861 |
| REFERENCE | 6: | 184:10862 |
| REFERENCE | 7: | 184:10863 |
| REFERENCE | 8: | 184:10864 |
| REFERENCE | 9: | 184:10865 |
| REFERENCE | 10: | 184:10866 |